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CADTH TECHNOLOGY REVIEW: OPTIMAL USE 360 REPORT

Anaplastic Lymphoma Kinase Inhibitors for Advanced Non-Small Cell Lung Carcinoma

Service Line:	Technology Review
Issue:	17
Publication Date:	February 2019
Report Length:	13 Pages

CADTH

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Cite as: Anaplastic Lymphoma Kinase Inhibitors for Advanced Non-Small Cell Lung Carcinoma. Ottawa: CADTH; 2019 Feb. (CADTH Technology Review: Optimal Use 360 Report; no. 17).

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ISSN: 2369-7385

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Background

Lung cancer is the second-most commonly diagnosed cancer in both men and women, and is the leading cause of cancer deaths in Canada.[1] Non-small cell lung carcinomas (NSCLC) are the most common type of lung cancer, comprising 85% of cases. In 2017, it is estimated that there were 28,600 new diagnosis of lung cancer and 21,100 deaths associated with lung cancer, with incidence and mortality rates of 59.4 and 45.3 out of 100,000, respectively.[1] The majority of patients with NSCLC will present with or develop advanced or metastatic disease. For these patients, the intent of treatment is to palliate symptoms and prolong survival. In patients with non-squamous NSCLC, the first step in determining treatment options is assessing of molecular markers, including chromosomal rearrangement of the anaplastic lymphoma kinase (ALK) gene on chromosome 2 (ALK-positive NSCLC). In these cases, the product of the fusion ALK gene acts as an oncogenic driver.[2] Although no national data are available for Canadian patients, the French Cooperative Thoracic Intergroup reported a 5% ALK positivity in patients with lung cancer assessed in the one-year period between April 2012 and April 2013.[3] Central nervous system metastases are quite common in ALK-positive lung cancers, presenting in up to 30 % of patients at diagnosis, and developing in more than 50% of patients initially treated with crizotinib at some point in their disease course.

Several small molecule inhibitors of ALK (ALKi) are or may soon become available in Canada. These include entrectinib, ceritinib, crizotinib, lorlatinib, alectinib, ensartinib, and brigatinib. See Appendix 1 for the regulatory status and approved indications of these products. Of note, some ALKi are indicated for first-line treatment of ALK-rearranged NSCLC or for treatment following progression on chemotherapy, while others are indicated only upon progression or failure with another ALKi.

In clinical practice, ALK inhibition is preferred over non-targeted therapies in ALK-positive NSCLC due to its effectiveness and favourable safety profile.[2] However, resistance to ALKi can develop at the genetic level. An alternate inhibitor is typically considered upon progression on a previous ALKi if it was proven to overcome resistance in this population. As a result, a relatively complex sequence of ALKi can be given to patients with ALK-positive NSCLC who develop resistance successively.

Policy Issue

Currently, crizotinib is the only ALK that is publicly funded by Canadian provinces and territories, while alectinib and ceritinib are under negotiation at the pan-Canadian Pharmaceutical Alliance table. The situation will soon become more complex with the anticipated arrival of three to four additional ALKi that are currently under advanced clinical investigation and/or pending regulatory approval. With the potential of a total of seven ALKi to be offered to naive or experienced patients, there will be a need to select, based on evidence of safety, effectiveness, cost-effectiveness, and patient values, which drug should be given first and what sequence of drugs should follow.

In order to inform funding algorithms, the pCODR Provincial Advisory Group, under the leadership of BC Cancer, has requested an overview of studies that compare ALK inhibitors to one another. To inform sequencing algorithms, it has also requested studies that examine the clinical effectiveness of ALK inhibitors in patients who failed (i.e., progressed on) other inhibitors of the same class.

The following policy questions were developed in consultation with BC Cancer:

1. Which ALKi should be preferentially funded for the treatment of ALKi-naive patients with ALK-positive locally advanced or metastatic NSCLC?
2. Which sequence of ALKi should be funded for ALK-positive locally advanced or metastatic NSCLC?

Purpose of This Report

The purpose of this CADTH Technology Review is to summarize the evidence findings regarding ALKi for NSCLC as identified by independent CADTH rapid health technology assessment (HTA) products, and to provide additional perspective, including an analysis of information gaps and further discussion on implications for decision-making, in order to assist the transition of current evidence into policy, practice, and future research.

Findings

The following CADTH Rapid Response reviews were commissioned to address the policy questions:

1. a Summary With Critical Appraisal of the clinical evidence on the relative safety and effectiveness of ALKi in treatment-naive and treatment-experienced patients
2. a Summary With Critical Appraisal of the cost-effectiveness of ALKi and associated evidence-based guidelines.

Table 1 provides key findings of the five studies meeting the inclusion criteria: one HTA, two systematic reviews, and two open-label randomized controlled trials (RCTs). Table 2 expands on the results from the meta-analysis by Fan et al.[4] regarding treatment-experienced patients. Table 3 provides findings from the identified four economic evaluations. Table 4 summarizes findings from the CADTH pan-Oncology Drug Review (pCODR) on alectinib and ceritinib, which are pertinent for the policy questions. Tabulated results are organized by policy questions. For detailed information on the study characteristics, results, and limitations, please refer to the Rapid Response reports published on the CADTH website:

Anaplastic Lymphoma Kinase Inhibitors for Genetically Rearranged Non-Small Cell Lung Cancer: A Review of the Clinical Effectiveness

https://cadth.ca/anaplastic-lymphoma-kinase-inhibitors-genetically-rearranged-non-small-cell-lung-cancer-review

Anaplastic Lymphoma Kinase (ALK) Inhibitors for Genetically Rearranged Non-Small Cell Lung Cancer: A Review of Cost-Effectiveness and Guidelines

https://cadth.ca/anaplastic-lymphoma-kinase-alk-inhibitors-genetically-rearranged-non-small-cell-lung-cancer-review-0

Table 1: Findings of the Clinical Studies Identified in the Rapid Response Report

Study	Comparisons	Key Findings
PQ1: What is the Preferred First Alki for NSCLC? [Alki-Naive Patients]		
EUnetHTA, 2018[5] Rapid HTA	Alectinib, crizotinib (ALEX trial)	Significantly longer **PFS** with alectinib. Lower frequencies of **treatment interruptions** and dose reductions with alectinib
Fan, 2018[4] NMA	Alectinib, ceritinib, crizotinib Mix of naive and experienced	**PFS:** Alectinib > ceritinib = crizotinib **Discontinuation:** Alectinib < ceritinib = crizotinib Other outcomes not significantly different
Gadgeel, 2018[6] RCT	Alectinib, crizotinib (ALEX trial, CNS results)	Superior **time to CNS progression** for alectinib
Camidge, 2018[7] RCT[a]	Brigatinib, crizotinib	Significantly longer **PFS** with brigatinib
PQ2: Optimal Alki Sequence [Alki–Pre-Treated Patients]		
Fan, 2018[4] Meta-analysis	Alectinib, brigatinib, ceritinib, ensartinib, lorlatinib ALKi (crizotinib) pre-treated patients	See Table 2
Zhao, 2018 [8] Meta-analysis	Ceritinib compared with chemotherapy in crizotinib–pre-treated patients	Significant ORR improvement Insignificant PFS and intracranial ORR improvement Other outcomes consistent with Fan (2018) [4]
Novello, 2018[9] RCT	Alectinib compared with chemotherapy in crizotinib–pre-treated patients (ALUR trial)	Statistically significant benefits for all outcomes except OS

ALKi = anaplastic lymphoma kinase inhibitors; CNS = central nervous system; HTA = health technology assessment; NMA = network meta-analysis; NSCLC = non-small cell lung carcinomas; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RCT = randomized controlled trial.

[a] This publication was identified in the appendix of the clinical review.

Table 2: Meta-Analysis Results for ALKi-Experienced NSCLC Patients (Fan, 2018)[4]

	PFS	ORR	ORR (CNS)	DCR	Discontinuation
Alectinib	✓	✓	✓	✓	✓
Ceritinib	✓[a]	✓	✓[a]	✓	✓
Brigatinib	✓	✓	✓	✓	✓
Lorlatinib	✓	✓	No data	✓	✓
Ensartinib	No data	✓	No data	✓	No data

ALKi = anaplastic lymphoma kinase inhibitors; CNS = central nervous system; DCR = disease control rate; NSCLC = non-small cell lung carcinomas; ORR = objective response rate; PFS = progression-free survival.

Note: Significant effects on outcomes (compared with conventional treatment) are marked with ✓.

Population is comprised of crizotinib-experienced advanced NSCLC patients.

[a] Zhao et al. (2018) meta-analysis reports non-significant PFS and ORR (CNS) for ceritinib.

Table 3: Findings of the Economic Studies Identified in the Rapid Response Report

Study	Comparisons	Key Findings
PQ1: What is the Preferred First Alki for NSCLC? [Alki-Naive Patients]		
Carlson, 2018[10]	Alectinib, crizotinib	Using a WTP threshold of US$100,000/QALY, alectinib was found to have a 64% probability of being cost-effective. Note that a reanalysis of this evaluation by pCODR[11] yielded lower probabilities.
Zhou, 2018[12]	Ceritinib, crizotinib	Incremental cost per QALY gained with ceritinib: US$66,064 /QALY. Ceritinib had a 76% probability of being cost-effective at a WTP of US$150,000/QALY.
PQ2: Optimal ALKi Sequence [Alki–Pre-Treated Patients]		
Carlson, 2017[13]	Alectinib, ceritinib	Alectinib treatment resulted in an ICER of US$31,180/QALY compared with ceritinib. Alectinib had a 96% probability of being cost-effective at a WTP of US$100,000/QALY.
Hurry, 2016[14]	Ceritnib, alternative non-ALKi treatment	ICER of C$149,117/QALY, C$80,100/QALY, and C$104,436/QALY in comparison with best supportive care, pemetrexed, and historical controls. Note that a reanalysis of this evaluation by pCODR[15] yielded higher ratios.

ALKi = anaplastic lymphoma kinase inhibitors; ICER = incremental cost-effectiveness ratio; NSCLC = non-small cell lung carcinomas; pCODR = CADTH pan-Canadian Oncology Drug Review; QALY = quality-adjusted life-year; WTP = willingness to pay.

Table 4: Findings of the pCODR Reviews on Anaplastic Lymphoma Kinase Inhibitors

Review	Comparisons	Key Findings
PQ1: Preferred First ALKi for NSCLC [ALKi-Naive Patients]		
pCODR 10125 Alecensaro for Non-Small Cell Lung Cancer (first line)[11]	Alectinib, crizotinib First-line treatment (Global-ALEX trial)	Alectinib associated with significantly higher PFS compared with crizotinib. Not cost-effective versus crizotinib. pERC recommends reimbursement, conditional on improved cost-effectiveness.
PQ2: Optimal ALKi Sequence [Alki–Pre-Treated Patients]		
pCODR 10094 Zykadia for Non-Small Cell Lung Cancer[15]	Ceritinib compared with chemotherapy in crizotinib–pre-treated patients (ASCEND-5 trial)	Statistically significant benefits in PFS for ceritinib. Increase in toxicity profile. Not cost-effective versus chemotherapy. pERC recommends reimbursement, conditional on improved cost-effectiveness.
pCODR 10114 Alecensaro for Locally Advanced or Metastatic NSCLC (second line)[16]	Alectinib compared with chemotherapy in crizotinib–pre-treated patients (ALUR trial) ITC with second-line ceritinib	Statistically significant benefits for all key outcomes except OS. Limited ITC. Cost-effective compared with chemotherapy. Not cost-effective compared with ceritinib (with caveats). pERC recommends reimbursement, conditional on improved cost-effectiveness.

ALKi = anaplastic lymphoma kinase inhibitors; ITC = indirect treatment comparison; NSCLC = non-small cell lung carcinomas; OS = overall survival; pCODR = CADTH pan-Canadian Oncology Drug Review; pERC = CADTH pCODR Expert Review Committee; PFS = progression-free survival.

Gap Analysis

Based on the sum of findings from the CADTH Rapid Response reports and pCODR reviews, comparisons (direct or indirect) have only been performed between alectinib, ceritinib, crizotinib, and brigatinib; of these, only the former three ALKi were analyzed together. Thus, only a subset of ALKi can be ranked using evidence-based, publicly available information. More RCTs and/or network meta-analyses (NMAs) comparing ALKi against each other are needed, preferably in ALKi-naive patients. Comparative studies did not always discriminate between ALKi-naive and experienced patients. The clinical relevance of pooling efficacy data from both patient populations will need to be validated. Finally, progression-free survival (PFS) appears to be the only variable that can be reliably compared across trials; its relevance in decision-making will need confirmation. No economic studies using results from multiple comparisons were found for helping with ranking.

When given to patients who were crizotinib-experienced, all ALKi (with the obvious exception of crizotinib) were found to be efficacious by at least one measure. Therefore, the evidence clearly indicates that other ALKi are (or will become) valid options after crizotinib therapy. However, evidence is unable to inform further sequencing algorithms given that all ALKi–pre-treated patients in identified trials had experience with crizotinib or some unspecified ALKi. No data on failure with other specific ALKi were found. Correspondingly, evidence-based guidelines identified in the CADTH reviews did not provide further advice on the optimal sequence of ALKi. For instance, the National Comprehensive Cancer Network guidelines on NSCLC[2] recommend alectinib as first-line therapy, but only provide recommendations regarding subsequent ALKi treatment for patients who have progressed on crizotinib, which is in line with the available clinical evidence.

As second-generation ALKi (such as alectinib) move to first-line treatment, the current clinical evidence will soon be unable to answer real-world sequencing questions, and more trials that include patients who have failed the new standard(s) of care will need to be conducted. In addition, evidence will be needed to clarify whether crizotinib can still play a role subsequent to the new first-line agents.

A medical librarian performed a search on Clinicaltrials.gov to identify ongoing studies that may help fill the abovementioned gaps. Only trials with the potential to address the gaps were included; replication trials, trials with a single first-line ALKi, and trials previously reviewed by CADTH were excluded. Please see Appendix 2 for search methods, including information sources and search approaches, and for a detailed list of ongoing trials.

In the next few years, clinical studies featuring head-to-head comparisons of ALKi in the first-line setting are set to be completed for brigatinib, ensartinib, and lorlatinib. Unfortunately, all will be compared with crizotinib, the standard ALKi at the time of trial initiation, but one unlikely to be the optimal comparator moving forward. A more complex, biomarker-driven trial (the NCI-NRG ALK Master Protocol)[17] will compare multiple ALKi, but is not due to be completed until much later. Furthermore, as the trial compares subsets of ALKi in subgroups of predefined patient groups harbouring specific genetic variants of ALK, it may not allow comparisons of ALKi in a broad, naive population that is not genetically characterized, limiting its relevance to the current policy and practice context.

A number of single-arm trials are investigating the effectiveness of next-generation ALKi in patients who are ALKi-experienced. Many include patients previously treated with alectinib or other next-generation ALKi, instead of crizotinib. Two trials feature groups of patients given crizotinib after progression with a newer ALKi.[18,19] These data may shed much needed light on the optimal sequencing of ALKi. However, the non-comparative design of the trials will limit the interpretability of the evidence. A single phase III RCT directly is comparing different ALKi in experienced patients, namely alectinib and brigatinib after treatment with crizotinib.[20]

Implications for Decision-Making

There is consensus among the evidence (namely CADTH HTAs, systematic reviews, clinical trials, economic studies, and guidelines) that the second-generation ALKi alectinib provides additional value relative to crizotinib and should be the preferred first-line treatment in clinical practice. In addition, an indirect comparison suggests that alectinib has superior efficacy versus ceritinib. However, given that ceritinib was not evaluated by pCODR for first-line treatment of NSCLC, this comparison has limited impact on decision-making.

Unlike alectinib, there are discrepancies regarding the value of ceritinib. The identified NMA concluded that crizotinib and ceritinib did not differ significantly in their impact on PFS. In contrast, an economic study demonstrated that ceritinib was likely cost-effective relative to crizotinib, in part due to superior efficacy. Data sources in the NMA and assumptions in the economic studies may explain this variation. Again, the relevance of these comparisons on decision-making is limited by the previously stated reasons.

There is scarce evidence comparing other emerging second- and third-generation ALKi such as brigatinib, entrectinib, and lorlatinib, with the exception of a single trial comparing brigatinib with crizotinib.[7] Therefore, should there be a clear need to rank ALKi for initial treatment, an NMA should be considered. This analysis should be based on a broad selection of studies, including single-arm, active control, and placebo controlled trials. Given the uncertainty around the approval of the newer drugs, one may have to wait for the most opportune time before proceeding.

There is published evidence of effectiveness for some second- and third-generation ALKi (alectinib, brigatinib, and ceritinib) in NSCLC patients who have failed on crizotinib. Translation of the latter findings into sequencing algorithms may be challenging should alectinib be preferred to crizotinib as the initial ALKi. Additional evidence on post-alectinib treatments may be emanating from trials that are currently in progress. Alternatively, it could be assumed that post-crizotinib PFS data are generalizable to any post-ALKi situation. Assumptions and/or clinical data could be used to build an economic model for identifying the optimal sequence of ALKi. Incorporating into an economic model any clinical information pertaining to sensitivity and/or resistance to ALKi based on refined genetic information, for the purpose of developing “personalized” care algorithms, may require the review of an expanded, possibly immature evidence base that would contribute high levels of uncertainty to the analysis.

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Appendix 1: Anaplastic Lymphoma Kinase Inhibitors

Generic (Brand) Name	Regulatory/HTA Status	Indication (Health Canada)	Development Stage
Crizotinib (Xalkori)	Approved by FDA, HC Recommended by pERC	Advanced ALK+ or ROS1+ NSCLC	Marketed
Alectinib (Alecensaro)	Approved by FDA, HC Recommended by pERC (first-line and after crizotinib)	Advanced ALK+ NSCLC	Marketed
Ceritinib (Zykadia)	Approved by FDA, HC Recommended by pERC (after crizotinib)	Advanced ALK+ NSCLC	Marketed
Brigatinib (Alunbrig)	Approved by FDA, HC (NOC/c)	Advanced ALK+ NSCLC having failed crizotinib	Marketed
Entrectinib	Data to be submitted to FDA, EMA	TBD	Phase II (pivotal) basket study for NTRK/ROS1/ALK
Lorlatinib	Under review by FDA, HC	TBD	Phase II (pivotal)
Ensartinib	Under development	TBD	Phase II

ALKi = anaplastic lymphoma kinase inhibitors; HC = Health Canada; HTA = health technology assessment; NOC/c = Notice of Compliance with condition; NSCLC = non-small cell lung carcinomas; NTRK = Neurotrophic tropomyosin receptor kinase; pERC = CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee; TBD = to be determined.

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Appendix 2: Ongoing Trials on Anaplastic Lymphoma Kinase Inhibitors

Search Methods

A limited literature search was conducted using the following bibliographic databases: MEDLINE, PubMed, Embase, and Cochrane Central Register of Controlled Trials. Grey literature was identified by searching relevant sections of the *Grey Matters* checklist: Clinical Trials Registries (https://www.cadth.ca/grey-matters). Randomized controlled trials and clinical studies were searched. The search was limited to English-language documents published between January 1, 2016, and December 6, 2018. Regular alerts updated the search until project completion.

Table 5: Ongoing Clinical Trials With Comparisons or Sequences Not Previously Reviewed by CADTH

Title	Drugs	Participants	Phase/Status	Primary Completion
First-Line Comparisons (Alki-Naive)				
Biomarker/ALK Inhibitor Combinations in Treating Patients With Stage IV ALK Positive Non-Small Cell Lung Cancer (The NCI-NRG ALK Master Protocol)	Alectinib Brigatinib Ceritinib Lorlatinib Ensartinib	660 grouped by ALK mutation	Phase II, open-label RCT Not yet recruiting	December 13, 2025
ALTA-1L Study: A Phase 3 Study of Brigatinib Versus Crizotinib in Anaplastic Lymphoma Kinase (ALK)-Positive Advanced Non-small Cell Lung Cancer (NSCLC) Participants	Brigatinib Crizotinib	275	Phase III, open-label RCT Active, not recruiting	July 31, 2020
eXalt3: Study Comparing X-396 (Ensartinib) to Crizotinib in ALK Positive Non-Small Cell Lung Cancer (NSCLC) Patients	Ensartinib Crizotinib	402	Phase III, open-label RCT Recruiting	April 2020
A Study Of Lorlatinib Versus Crizotinib In First Line Treatment Of Patients With ALK-Positive NSCLC	Lorlatinib Crizotinib	280	Phase III, open-label RCT Recruiting	December 31, 2020
Subsequent Line (ALKi-Experienced)				
An Efficacy Study Comparing Brigatinib Versus Alectinib in Advanced Anaplastic Lymphoma Kinase-Positive Non-Small-Cell Lung Cancer Participants Who Have Progressed on Crizotinib	Alectinib Brigatinib	246	Phase III, open-label RCT Not yet recruiting	October 29, 2021
A Study of Brigatinib in Participants With Anaplastic Lymphoma Kinase-Positive (ALK+), Advanced Non-Small-Cell Lung Cancer (NSCLC) Progressed on Alectinib or Ceritinib	Brigatinib	103	Phase II, single-arm Not yet recruiting	December 18, 2019
Trial of Brigatinib After Treatment With Next-Generation ALK Inhibitors	Brigatinib	120	Phase II, single-arm Recruiting	January 2020
A Study to Evaluate the Efficacy of Brigatinib (AP26113) in Participants With Anaplastic Lymphoma Kinase (ALK)-Positive, Non-small Cell Lung Cancer (NSCLC) Previously Treated With Crizotinib	Brigatinib (2 doses)	222	Phase II, open-label RCT Active, not recruiting	February 29, 2016
LDK378 in Patients With ALK Positive NSCLC Previously Treated With Alectinib.	Ceritinib	20	Phase II, single-arm Completed	May 24, 2018
A Study Of PF-06463922 An ALK/ROS1 Inhibitor In Patients With Advanced Non Small Cell Lung Cancer With Specific Molecular Alterations	Lorlatinib Crizotinib (following failure)	334	Phase I/II, single-arm Active, not recruiting	March 15, 2017

Title	Drugs	Participants	Phase/Status	Primary Completion
Efficacy of crizotinib in alectinib-refractory patients with NSCLC harboring EML4-ALK; phaseII trial (OLCSG1405)	Crizotinib (following alectinib failure)	9	Phase II, single-arm Recruiting	Unknown
X-396 Capsule in Patients With ALK-positive Non-small Cell Lung Cancer Previously Treated With Crizotinib	Ensartinib	152	Phase II, single-arm Recruiting	December 2018

ALK = anaplastic lymphoma kinase; ALKi = anaplastic lymphoma kinase inhibitors; RCT = randomized controlled trial.